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Iodine Maps from Subtraction CT or Dual-Energy CT to Detect Pulmonary Emboli with CT Angiography: A Multiple-Observer Study

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Conflicts of interest are listed at the end of this article.

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Background: Dual-energy CT iodine maps are used to detect pulmonary embolism (PE) with CT angiography but require dedicated hardware. Subtraction CT, a software-only solution, results in iodine maps with high contrast-to-noise ratios.

Purpose: To compare the use of subtraction CT versus dual-energy CT iodine maps to CT angiography for PE detection.

Materials and Methods: In this prospective study (*https://clinicaltrials.gov*, NCT02890706), 274 participants suspected of having PE underwent precontrast CT followed by contrast material–enhanced dual-energy CT angiography between July 2016 and April 2017. Iodine maps from dual-energy CT were derived. Subtraction maps (contrast-enhanced CT minus precontrast CT) were calculated after motion correction. Truth was established by expert consensus. A total of 75 randomly selected participants with and without PE (1:1 ratio) were evaluated by three radiologists and six radiology residents (blinded to final diagnosis) for the presence of PE using three types of CT: CT angiography alone, dual-energy CT, and subtraction CT. The partial area under the receiver operating characteristic curve (AUC) for the clinically relevant specificity region (maximum partial AUC, 0.11) was compared by using multireader multicase variance. A P value less than or equal to .025 was considered indicative of a significant difference due to multiple comparisons.

Results: There were 35 men and 40 women in the reader study (mean age, 63 years ± 12 [standard deviation]). The pooled sensitivities were not different ($P \geq .31$ among techniques) (95% confidence intervals [CIs]: 67%, 89% for CT angiography; 72%, 91% for dual-energy CT; 70%, 91% for subtraction CT). However, pooled specificity was higher for subtraction CT (95% CI: 100%, 100%) than for CT angiography (95% CI: 89%, 97%) or dual-energy CT (95% CI: 89%, 98%) ($P < .001$). Partial AUCs for the average observer improved equally when adding iodine maps (subtraction CT [0.093] vs CT angiography [0.088], $P = .03$; dual-energy CT [0.094] vs CT angiography, $P = .01$; dual-energy CT vs subtraction CT, $P = .68$). Average reading times were equivalent (range, 97–101 seconds; $P \geq .41$) among techniques.

Conclusion: Subtraction CT iodine maps had greater specificity than CT angiography alone in pulmonary embolism detection. Subtraction CT had comparable diagnostic performance to that of dual-energy CT, without the need for dedicated hardware.

Online supplemental material is available for this article.

Pulmonary embolism (PE) represents a prevalent acute cardiovascular condition that has considerable morbidity and mortality and requires prompt diagnosis and treatment (1). Since 2007, multidetector CT pulmonary angiography has been the standard technique used to detect PE (2), achieving sensitivity and specificity (3–5) higher than 90% with state-of-the-art equipment (6). A missed PE carries a high potential risk for a future venous thromboembolism. On the other hand, false-positive results and subsequent anticoagulation treatment can result in complications (7). The potential for overdiagnosis of PE is as harmful as underdiagnosis (8).

Iodine maps depict abnormalities that correspond to loss of blood flow caused by an acute (or chronic) PE (9–12). Iodine maps improve sensitivity in the detection of emboli, especially small emboli at a subsegmental level or in more distal vessels (13,14) and support prognosis determination and monitoring of anticoagulation therapy effectiveness (15).

The most common technique used to generate these maps is dual-energy CT (16,17). However, this requires dedicated hardware. On the other hand, subtraction CT requires motion correction software but no additional hardware, making it easier to adopt and less costly to

Abbreviations

AUC = area under the ROC curve, CI = confidence interval, DLP = dose-length product, PE = pulmonary embolism, ROC = receiver operating characteristic

Summary

Subtraction CT shows diagnostic performance comparable to that of dual-energy CT in the detection of pulmonary embolism at similar radiation dose, without the need for dedicated hardware.

Key Points

- Subtraction CT showed higher specificity (100%) in the detection of pulmonary embolism (PE) compared with CT angiography alone (94%) and dual-energy CT (95%) ($P < .001$).
- Iodine maps had a small added value in PE detection compared with CT angiography alone (partial area under the receiver operating characteristics curve was 0.094 for dual-energy CT, 0.093 for subtraction CT, and 0.088 for CT angiography; *P* values ranged from .01 to .03).
- Reading times did not increase when iodine maps were added to CT angiography (CT angiography alone, 97 seconds; dual-energy CT, 101 seconds; subtraction CT, 99 seconds; $P \geq .41$ among techniques).

implement in clinical practice. It digitally subtracts a precontrast CT scan from a contrast material–enhanced CT scan after motion correction (18,19). This approach results in a contrast-to-noise ratio higher than that with dual-energy CT due to the use of the entire difference between iodine-perfused and precontrast injection tissue attenuation, rather than the spectral decomposition of water (tissue) from iodine, as in dual-energy CT (20,21). The smaller signal difference between the two dual-energy scans as compared with that between the precontrast and contrast-enhanced scans in subtraction CT at the same noise levels results in the output dual-energy CT iodine map having approximately half the contrast-to-noise ratio as that of the subtraction CT iodine map. Given the demonstrated benefit of dual-energy CT iodine maps in the detection of PE, it is of interest to determine if subtraction CT–derived iodine maps have the same or a superior added value. A previous study showed an observer preference for and a higher signal difference–to-noise ratio of subtraction CT when compared with dual-energy CT at a lower total radiation dose (22). However, it is unclear whether this improvement in image quality translates into better efficacy for PE detection. Our hypothesis was that subtraction CT would be comparable to dual-energy CT in the detection of PE. The purpose of this observer study was to compare adding subtraction or dual-energy iodine maps to CT angiography in pulmonary embolism detection.

Materials and Methods

Study Population

This prospective study was approved by the regional ethical review board (NL56542.091.16, *https://clinicaltrials.gov* NCT02890706) and involved the recruitment and imaging of 295 consecutive study participants after obtaining written informed consent at the Meander Medical Centre between July 2016 and April 2017. Canon Medical Systems provided financial funding and the CT subtraction software. The authors had control of all data and information throughout the study.

Patients undergoing clinical dual-energy CT pulmonary angiography for suspicion of PE at the Meander Medical Centre were eligible for inclusion. At this clinical site, patients are referred for dual-energy CT according to the Wells criteria (23), excluding pregnant women and women younger than 35 years because of concerns about breast irradiation. The sole inclusion criterion was that patients could provide written informed consent. Exclusion criteria were *(a)* hemodynamic instability and *(b)* male patients younger than 35 years (to match the female patient population).

A detailed description of the sample size calculation is included in Appendix E1 (online). A subset of the resulting images was used in our previous study, in which we compared the image quality of the subtraction CT and dual-energy CT iodine maps (22). This involved a subjective image quality comparison using the first 60 participants included in the present study and the objective comparison of iodine enhancement in 29 participants with acute PE. Thus, the patient population in the present study has an overlap of 86 participants with a previous study; however, it involves a different analysis of the data, since no diagnostic performance measures were obtained or compared.

CT Scan Protocol

Study participants underwent dual-energy CT angiography (Definition Flash; Siemens Healthineers, Forchheim, Germany) of the chest for clinical evaluation according to standard clinical practice in the Meander Medical Center (100 kV, 140 kV and tin filter) and a precontrast scan specifically for our current study (100 kV). A detailed description of the CT protocol is given in Appendix E1 (online). Breathing instructions were the same for all examinations.

Image Reconstruction and Iodine Map Generation

The precontrast image and contrast-enhanced dual-energy CT images were reconstructed using an iterative dual-energy reconstruction kernel (Q30f) at 1-mm thickness with sinogram-affirmed iterative reconstruction. The dual-energy CT iodine maps were generated using the Lung Analysis application of the Syngo.via workstation (D.G.) (version 3, Siemens Healthineers) with default blending. To obtain the subtraction CT iodine maps, arithmetic subtraction of the precontrast image from the contrast-enhanced image was performed (L.O., D.G.) using the 100-kV dual-energy CT acquisition after motion correction using the $^{\text{SURE}}$Subtraction lung algorithm (version 8; Canon Medical Systems, Otawara, Japan). Both the subtraction image and the dual-energy iodine map were color coded in the same manner for presentation to the readers.

Data Collection and Reference Standard

All study participants underwent treatment according to standard local clinical practice. Participant data—including age, pulmonary embolism severity index (or PESI) score, potential alternative diagnosis, and adverse events—and all imaging data were extracted from the electronic medical records and from the picture archiving and communication system (Impax, version 6.6; Agfa HealthCare, Mortsel, Belgium). If participants were clinically discharged from follow-up, they were contacted by phone (D.G.) after 6 months to fill out a questionnaire based on Krestan et al (24). Patients were called a maximum of three times, and if they were still unreachable, the questionnaire was marked "not available." Radiation dose for all three scans (pre- and postcontrast 100 kV, postcontrast 140 kV), with dose-length product (DLP) as the representative metric, were extracted from the Digital Imaging and Communications in Medicine radiation dose structured report, and combined, as appropriate, to obtain the DLP resulting from subtraction CT, dual-energy CT, and CT angiography examinations.

Three board-certified radiologists (M.P., C.S.P., M.B.) with 25, 28, and 8 years of experience, respectively, in thoracic radiology and clinical expertise in either subtraction (M.P., M.B.) or dual-energy (C.S.P.) CT with access to all participant clinical and imaging data, including the iodine maps (unblinded), provided the reference standard for the diagnosis or exclusion of PE in consensus, as described in Appendix E1 (online). Finally, one radiologist (M.B.) annotated segmental and subsegmental (peripheral) location of the PE.

Observer Study

We assembled an enriched case data set, with each case consisting of a combination of images making up one of the three index tests (CT angiography only, CT angiography in addition to CT angiography with overlaid dual-energy iodine map, and CT angiography in addition to CT angiography with overlaid subtraction iodine map) from a random selection of 37 participants with PE and 38 participants without PE. The cases of an additional 10 participants, five with PE and five without PE, were used for training at the beginning of each observer session to get the observers used to the user interface, the workstation, and the requested task. Two radiologists with experience in subtraction CT (M.S., B.G.; 15 years and 7 years of experience in thoracic radiology, respectively), one radiologist with experience in dual-energy CT (R.D., 8 years), three radiology residents with experience in dual-energy CT (L.S., J.P., J.K.; 4, 2, and 2 years, respectively), and three residents with experience in subtraction CT (E.S. and two others, 4, 4, and 3 years of experience, respectively) participated as observers. All observers were aware of our inclusion criteria and the enriched nature of the data set but did not know the prevalence of PE. They were blinded to all other clinical data, including participant history and follow-up, and to the technique used to create each iodine map by using the same color scale for all iodine maps.

All observers interpreted results of the three index tests in all 75 participants three times over three sessions at an in-house dedicated scoring workstation (CIRRUS Essentials 2018) with at least a 4-week interval between sessions. During each session, all 75 cases were shown, 25 per technique, with cases and techniques in a randomized order.

For each case, each observer was asked to provide a binary decision on the presence or absence of PE and to provide a level of suspicion about the presence of PE on a five-point Likert scale (1, definitely PE present; 5, definitely no PE). The scoring workstation software recorded the reading time for each case.

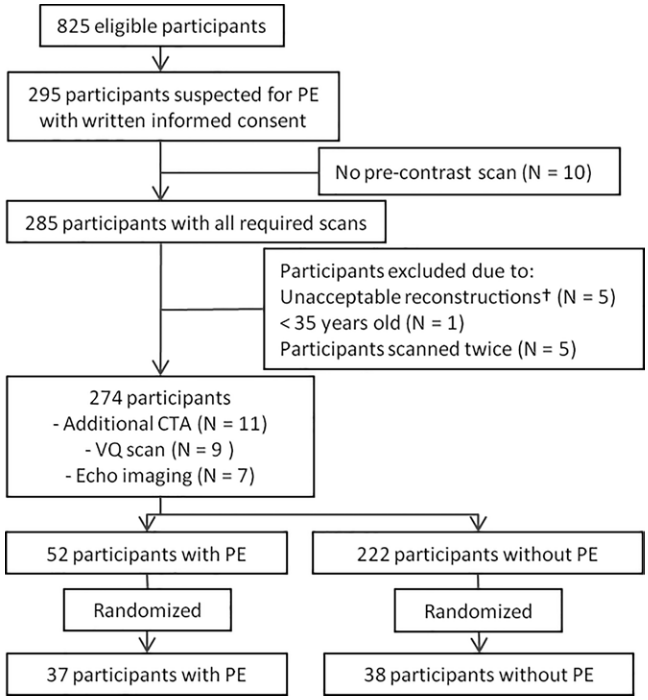

Figure 1: Flowchart shows the final observer study cohort. † The precontrast scans were not reconstructed according to the research requirements for our study (3-mm sections were reconstructed instead of 1-mm sections), and the raw data had already been removed from the CT workstation when this was noticed. CTA = CT angiography, PE = pulmonary embolism, VQ = ventilation-perfusion scan.

Statistical Analysis

The binary decision on the presence of PE was used to determine sensitivity and specificity, while receiver operating characteristic (ROC) curves were estimated for all observers from the level of suspicion ratings. Pooled sensitivity and specificity, including 95% confidence intervals (CIs), were estimated with generalized estimated equations using a commercially available statistics program (SPSS, version 22; IBM, New York, NY). Binormal ROC analysis was performed using the Obuchowski-Rockette and Dorfman-Berbaum-Metz multireader multicase variance analysis (25) (OR-DBM MRMC, version 2.5; University of Iowa, Iowa City, Ia) to obtain the area under the ROC curve (AUC) per technique and per observer. Given the expected very high specificity (14,26,27), partial AUC was calculated. The lowest value of the 95% CI of specificity was used for the cutoff value of the partial AUC.

An unpaired *t* test was used to test whether years of experience differed between observers who used dual-energy CT and those who used subtraction CT and also to define any difference in sensitivity and specificity between radiologists and residents for each technique. Radiation dose for each technique was represented by the median DLP with the 95% CI and was compared by using a paired *t* test. Average reading time per case averaged across all observers was calculated and compared with a paired *t* test. The analysis of variance test was used to detect whether there was any difference in reading time per case between modalities over the three sessions. Finally, observer agreement in the presence of PE for each technique was calculated by using

Table 1: Demographic Characteristics of Study Participants

Characteristic	Entire Cohort (n = 274)	Participants included in the Observer Study (n = 75)	Participants with PE included in the Observer Study (n = 37)
Age (y)*	63.4 ± 12.2	63.5 ± 11.4	63.2 ± 10.0
Sex	124 men, 150 women	35 men, 40 women	18 men, 19 women
Coexisting condition			
PESI score*	85.9 ± 26.7	88.9 ± 25.7	89.2 ± 25.0
History of cancer	80/274 (29)	26/75 (35)	12/37 (32)
History of heart failure	13/274 (5)	5/75 (7)	2/37 (5)
History of chronic lung disease	91/264 (34)	22/75 (29)	11/37 (30)
Heart rate >110 bpm	31/263 (12)	10/71 (14)	6/35 (17)
Systolic blood pressure <100 mmHg	5/262 (2)	2/71 (3)	1/35 (3)
Respiratory rate >30 breaths per minute	1/265 (1)	0/71 (0)	0/35 (0)
Temperature <36°C	4/263 (2)	1/71 (1)	0/35 (0)
Altered mental status	4/268 (1)	2/71 (3)	1/35 (3)
O_2 saturation <90%	17/252 (7)	5/70 (7)	4/35 (11)
Death within 6 months	20/274 (7)	6/75 (8)	3/37 (8)
Follow-up			
By electronic record	201/274 (73)	63/75 (84)	33/37 (89)
By questionnaire	54/274 (19)	9/75 (12)	3/37 (11)
Lost to follow-up	19/274 (7)	3/75 (4)	1/37 (3)

Note.—Unless otherwise indicated, data are numbers of patients (numerator/denominator), with percentages in parentheses. PE = pulmonary embolism, PESI = pulmonary embolism severity score.

* Data are mean ± standard deviation. In some cases, data were not available for all participants.

the Fleiss κ test. Bonferroni correction was used to determine statistical significance due to multiple comparisons. We used $P < .025$ to indicate statistical significance for all statistical tests.

Results

Figure 1 is the patient flowchart and shows the eligible participants, number of study participants, number of participants excluded after imaging, and final study cohort. None of the subtraction CT scans were excluded because of inadequate registration, and none of the precontrast CT examinations had to be repeated. None of the dual-energy CT angiography scans had inadequate contrast opacification. Of 75 study participants in the observer study, 37 (49%) had a confirmed pulmonary embolus. Participants had an average age of 64 years, 35 were men (47%), and 39 (49%) had a history of cancer, chronic lung disease, or both (Table 1). A total of 63 participants were clinically observed by their physician for 6 months. In total, 10 participants were observed with this questionnaire (mean age, 62 years; two men), two of whom had findings positive for PE. During the consensus review process, the results from the questionnaire were used only once to reach a decision. None of the two patients with unavailable questionnaires had equivocal cases at consensus review. When compared with the results of the clinical evaluation, there was a discrepancy between the radiologic report and the expert panel decision in six patients. This is described in Appendix E1 (online).

Observer Performance for Detection of PE

Tables 2 and 3 show sensitivity and specificity per technique and per observer. For the average observer, the addition of iodine maps did not result in higher sensitivity (P = .31 for both iodine maps compared with CT angiography). Specificity was not higher with dual-energy CT than with CT angiography alone (P = .17) but was higher with the addition of subtraction CT ($P < .001$).

Tables 4 and 5 show the AUC and partial AUC for each technique per observer and for the average observer. The partial AUC cutoff threshold was set at 0.11, given the obtained lower end of the 95% CI was 89% for specificity with CT angiography and dual-energy CT. As can be seen, the ROC curves for all three techniques are similar, without any significant difference (P = .10 for subtraction CT vs CT angiography, P = .12 for dual-energy CT vs CT angiography) (Fig 2). The partial AUC results show higher accuracy for both subtraction CT and dual-energy CT when compared with CT angiography, but only dual-energy CT was significant (subtraction CT, P = .03; dual-energy CT, P = .01) (Fig 2). As shown in Table 4, experience with a specific iodine technique was not predictive of a higher AUC for that technique for seven of the nine observers. Figure 3 shows an example case with a PE that was missed by more observers at CT angiography alone than at subtraction CT and dual-energy CT. Figure 4 shows a scan without PE with suboptimal contrast enhancement. In this case, the observers made the correct diagnoses more often with subtraction CT than with the other two techniques.

Other Outcome Parameters

There was no significant difference in experience between dual-energy CT observers and subtraction CT observers

Table 2: Sensitivity of Each Technique in Pulmonary Embolism Detection

Observer and Experience	CT Angiography (%)	DE CT (%)	Subtraction CT (%)
Sensitivity of the average observer (%)*	80 (67, 89)	85 (72, 92)	83 (70, 91)
Observer 1, DE CT	73 (27/37)	78 (29/37)	73 (27/37)
Observer 2, subtraction CT	81 (30/37)	84 (31/37)	78 (29/37)
Observer 3, subtraction CT	86 (32/37)	86 (32/37)	89 (33/37)
Observer 4, DE CT	76 (28/37)	84 (31/37)	86 (32/37)
Observer 5, DE CT	81 (30/37)	78 (29/37)	78 (29/37)
Observer 6, DE CT	81 (30/37)	86 (32/37)	81 (30/37)
Observer 7, subtraction CT	78 (29/37)	81 (30/37)	81 (30/37)
Observer 8, subtraction CT	81 (30/37)	86 (32/37)	86 (32/37)
Observer 9, subtraction CT	81 (30/37)	92 (34/37)	86 (32/37)

Note.—Unless otherwise indicated, data are sensitivity, with numerators and denominators in parentheses. P values were as follows: $P = .31$ for CT angiography versus subtraction CT, $P = .31$ for CT angiography versus DE CT, and $P > .9$ for subtraction CT versus DE CT. $P < .025$ indicates a significant difference between the techniques. DE CT = dual-energy CT.

* Data in parentheses are 95% confidence intervals.

Table 3: Specificity of Each Technique in Pulmonary Embolism Detection

Observer and Experience	CT Angiography (%)	DE CT (%)	Subtraction CT (%)
Specificity of the average observer*	94 (89, 97)	95 (89, 98)	100 (100, 100)
Observer 1, DE CT	97 (37/38)	92 (35/38)	100 (38/38)
Observer 2, subtraction CT	97 (37/38)	97 (37/38)	100 (38/38)
Observer 3, subtraction CT	95 (36/38)	97 (37/38)	100 (38/38)
Observer 4, DE CT	84 (32/38)	74 (28/38)	92 (35/38)
Observer 5, DE CT	95 (36/38)	97 (37/38)	97 (37/38)
Observer 6, DE CT	95 (36/38)	95 (36/38)	97 (37/38)
Observer 7, subtraction CT	95 (36/38)	97 (37/38)	100 (38/38)
Observer 8, subtraction CT	92 (35/38)	97 (37/38)	100 (38/38)
Observer 9, subtraction CT	87 (33/38)	89 (34/38)	97 (37/38)

Note.—Unless otherwise indicated, data are sensitivity, with numerators and denominators in parentheses. P values were as follows: $P < .001$ for CT angiography versus subtraction CT, $P = .17$ for CT angiography versus DE CT, and $P < .001$ for subtraction CT versus DE CT. $P < .025$ indicates a significant difference between the techniques. DE CT = dual-energy CT.

* Data in parentheses are 95% confidence intervals.

($P = .38$), nor was there a difference between radiologists and residents in sensitivity or specificity for each technique (lowest P value was .05 for specificity of CT angiography, with an overall P value range of .05 to .94). Interobserver agreement was 0.77 for CT angiography and 0.80 for dual-energy CT, reflecting substantial agreement, and 0.86 for subtraction CT, indicating almost perfect agreement. Median DLP was 97.4 mGy·cm (95% CI: 92 mGy·cm, 104 mGy·cm) for CT angiography, 177.4 mGy·cm (95% CI: 166 mGy·cm, 186 mGy·cm) for dual-energy CT ($P < .001$ vs CT angiography), and 165.8 mGy·cm (95% CI: 157 mGy·cm, 177 mGy·cm) for subtraction CT ($P < .001$ vs CT angiography, $P < .001$ vs dual-energy CT).

Overall reading times were 97 seconds for CT angiography, 101 seconds for dual-energy CT ($P = .41$ vs CT angiography), and 99 seconds for subtraction CT ($P = .61$ vs CT angiography, $P = .67$ vs dual-energy CT). Additional detailed results are included in Appendix E1 (online).

Discussion

Subtraction CT is an alternative to dual-energy CT for use in iodine mapping of the lungs in patients with pulmonary embolism (PE) that does not require the hardware that is necessary for dual-energy CT. Subtraction CT, a software-only solution, can generate iodine maps on potentially any CT scanner. Our study shows that the addition of iodine maps resulted in a small improvement in diagnostic performance beyond that obtained with CT angiography alone. This improvement in performance was due to an increase in specificity (subtraction CT, 100%; dual-energy CT, 95%; CT angiography alone, 94%; $P < .001$), while sensitivity was not higher for subtraction CT (83%) or dual-energy CT (85%) when compared with that of CT angiography alone (80%) ($P \geq .31$). Higher specificity could be helpful in reducing the overdiagnosis of PE. In addition, average reading times were similar for subtraction CT compared with nonsubtraction methods (CT angiography

Table 4: AUC for Each Technique

Observer and Experience	CT Angiography	DE CT	Subtraction CT
AUC for the average observer	0.93 (0.88, 0.97)	0.94 (0.90, 0.98)	0.94 (0.90, 0.99)
Observer 1, DE CT	0.92	0.93	0.92
Observer 2, subtraction CT	0.93	0.95	0.94
Observer 3, subtraction CT	0.97	0.95	0.98
Observer 4, DE CT	0.88	0.92	0.93
Observer 5, DE CT	0.92	0.92	0.92
Observer 6, DE CT	0.93	0.95	0.95
Observer 7, subtraction CT	0.95	0.94	0.94
Observer 8, subtraction CT	0.93	0.96	0.96
Observer 9, subtraction CT	0.91	0.96	0.96

Note.—Data are AUCs. Data in parentheses are 95% confidence intervals. P values were as follows: P = .10 for CT angiography versus subtraction CT, P = .12 for CT angiography versus DE CT, and P = .93 for subtraction CT versus DE CT. $P < .025$ indicates a significant difference between the techniques. AUC = area under the receiver operating characteristics curve, DE CT = dual-energy CT.

Table 5: Partial AUC for Each Technique

Observer and Experience	CT Angiography	DE CT	Subtraction CT
Partial AUC for the average observer	0.088 (0.08, 0.10)	0.094 (0.08, 0.11)	0.093 (0.08, 0.10)
Observer 1, DE CT	0.09	0.09	0.09
Observer 2, subtraction CT	0.09	0.10	0.09
Observer 3, subtraction CT	0.10	0.10	0.10
Observer 4, DE CT	0.09	0.10	0.09
Observer 5, DE CT	0.09	0.09	0.09
Observer 6, DE CT	0.08	0.09	0.08
Observer 7, subtraction CT	0.09	0.09	0.09
Observer 8, subtraction CT	0.09	0.10	0.10
Observer 9, subtraction CT	0.09	0.10	0.09

Note.—Data are partial area under the receiver operating characteristics curve. Data in parentheses are 95% confidence intervals. P values were as follows: P = .03 for CT angiography versus subtraction CT, P = .01 for CT angiography versus DE CT, and P = .65 for subtraction CT versus DE CT. $P < .025$ indicates a significant difference between the techniques. AUC = area under the receiver operating characteristics curve, DE CT = dual-energy CT.

alone, 97 seconds; dual-energy CT, 101 seconds; subtraction CT, 99 seconds; P = .41 among techniques).

On the basis of prior studies, we had expected there might be a small increase in sensitivity for PE because of the addition of iodine maps from subtraction CT. However, much larger studies may be required to detect improved sensitivity. For example, a recent large retrospective study of 1144 consecutive dual-energy CT examinations found that the number of new PEs diagnosed using iodine maps was only 2.3% of the examinations, resulting in new diagnosis of PE in 1.1% of the patients (28). Our study was powered to detect a difference in accuracy based on the results of previous studies on dual-energy CT iodine maps, which are quite diverse in terms of study group size and reference standard. Nevertheless, these studies uniformly found an accuracy improvement using the iodine maps.

There are several reports that show some improvement of sensitivity for PE with dual-energy iodine maps. One study of 83 participants (14) showed lower sensitivity of CT angiography versus dual-energy CT (observer 1, 85.5% vs 97.6%; observer 2, 90.4% vs 95.1%). However, that study excluded cases with motion artifacts and chronic PE, both of which are known to decrease the accuracy of dual-energy CT for acute PE. Another feasibility study of 24 participants in which only four participants had findings positive for PE (29) reported sensitivity and specificity in the detection of PE with dual-energy CT angiography of 100% on a per-patient basis for both observers. In that study, the reference standard was a third observer who only had CT angiography results available as the reference standard. In contrast to these results, Thieme et al (30) reported a lower sensitivity (75%) and specificity (80%) on a per-patient basis with dual-energy CT when compared with our study. They used planar ventilation-perfusion scintigraphy with technetium 99–labeled macroaggregated albumin as the reference standard, with a median follow-up time of 3 days (range, 0–90 days) between dual-energy CT and the reference test.

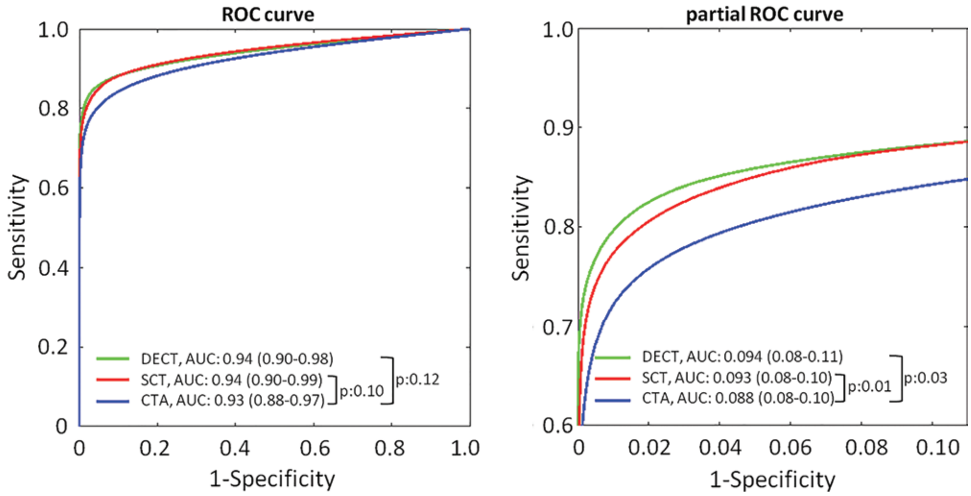

Figure 2: The entire (left) and partial (right) pooled receiver operating characteristic (ROC) curves show the detection performance of CT angiography (CTA), dual-energy CT (DECT), and subtraction CT (SCT). The values show the area under the ROC curve (AUC) or the partial AUC of the three techniques, with the 95% confidence interval in parentheses and relevant *P* values. The partial ROC curve highlights the difference in performance in the region where specificity has the largest differences between the techniques.

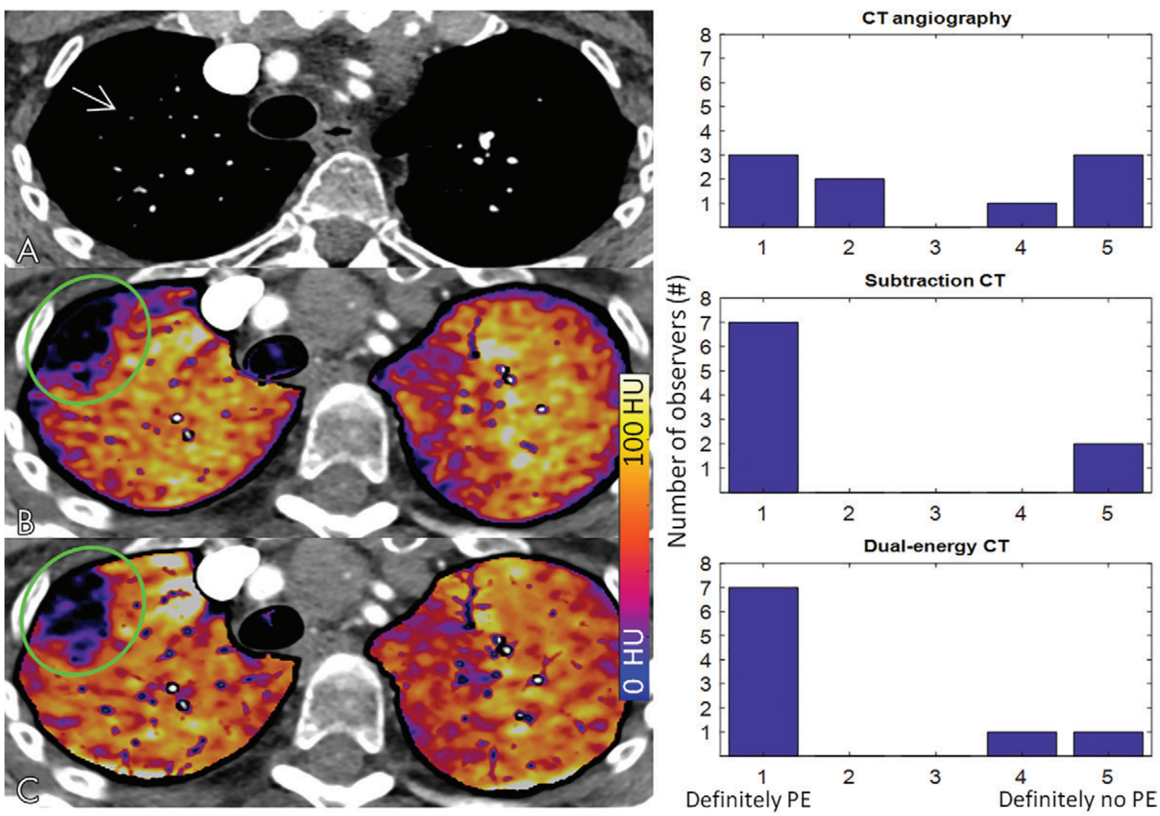

Figure 3: Images in a 79-year-old woman with segmental pulmonary embolism (PE) in the right upper lobe were obtained with, *A,* CT angiography, *B,* subtraction CT, and, *C,* dual-energy CT. All images are shown in the 1-mm axial view. The presence of PE (arrow in *A*) was missed by four observers at CT angiography. Both iodine maps (*B* and *C*) show the large perfusion defect caused by this embolus with perfusion defect (green circle). With the addition of either iodine map, the PE was missed by only two observers. The level of suspicion ratings are shown in the histograms next to the image acquired with that technique and show that the observers assigned the score *definitely PE* more often with subtraction CT and dual-energy CT.

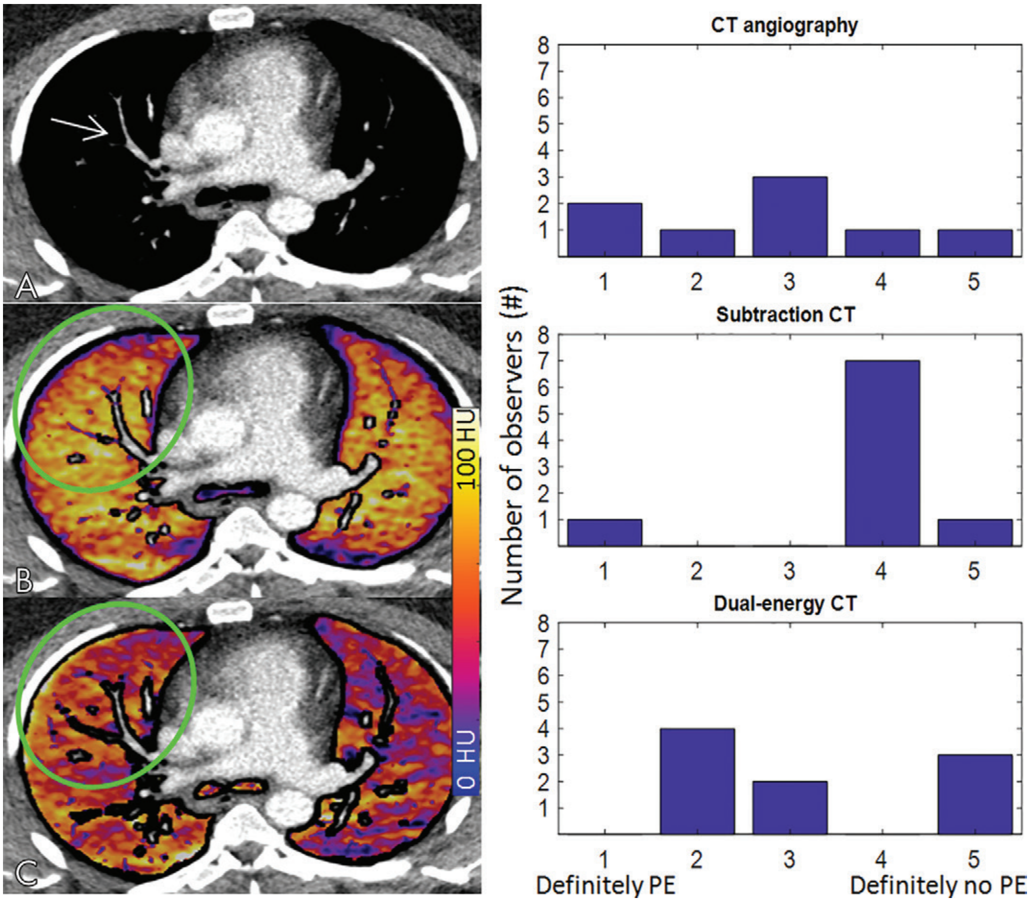

Figure 4: Axial images (1-mm sections) in a 39-year-old woman without pulmonary embolism (PE). *A*, CT angiogram shows poor contract enhancement in the blood vessels (arrow). *B*, Subtraction CT image with related perfusion map of the vessel in *A* (green circle). *C*, Dual-energy CT image with related perfusion map of the vessel in *A* (green C). Enhancement was 216 HU in the pulmonary trunk. Five of the nine observers rated this case positive at CT angiography; six rated it as positive at dual-energy CT, and one observer rated it as positive at subtraction CT. The level of suspicion is shown in histograms next to each image.

We did not use any selection criteria in terms of underlying disease or imaging quality. In that respect, our study cohort is representative of routine clinical practice. We explicitly selected observers with different levels of experience to allow for more generalizable results. In addition to improving the detection of PE, dual-energy CT was shown to help reduce the iodine load in the PE scan protocol (31). Subtraction CT holds the same potential but requires perfect registration of small vessels to do so.

Our study had some limitations. First, our reference standard was obtained by expert consensus with access to all participant data as opposed to an independent objective reference standard. Second, the sample size of the observer study was limited, but we were able to draw conclusions for the calculated average observer. Finally, our study was performed as a standard ROC study, with no location information of the perceived PE considered. Thus, a true-positive case could have been the result of a false-positive perceived PE in a different location than the true PE. However, since PE treatment involves systemic medication, this limitation is clinically irrelevant with the exception of the case of a missed solitary subsegmental PE and a false-positive PE in a larger branch. In such a case, medication would be given despite our clinical guidelines that suggest withholding treatment in these patients. In this study, only two participants had a solitary subsegmental PE, and indeed these patients did not undergo treatment. Observers scored these cases with low sensitivity overall, and there were no clear differences in performance among techniques. Overall, it shows that CT is able to show all PEs and not only clinically relevant PEs, which is a potential limitation of the study.

In conclusion, subtraction and dual-energy CT iodine maps show a small improvement compared with CT angiography in the detection of pulmonary embolism without requiring longer reading times. Both iodine map techniques did not show significant improvement for sensitivity. However, subtraction CT had a significantly higher specificity compared with CT angiography. We show that subtraction CT has a comparable diagnostic performance to dual-energy CT in the detection of pulmonary embolism at a similar radiation dose and without the need for dedicated hardware.

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